

ORIGINAL ARTICLE

Fixation in Patients with Juvenile Macular Disease

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ABSTRACT

Purpose. The instability of fixation with central scotoma has been mainly studied in patients with age-related macular diseases (MDs). However, early macular lesions can lead to different characteristics of fixation. The aim of this work was to study fixation in patients with juvenile MD.

Methods. Eye movements of 10 patients and 10 controls were monitored during fixation. Visual fields were assessed by static perimetry to determine the extent of the field defects. Eye movements were separated into saccades and drifts, with fixation stability assessed by bivariate contour ellipse area (BCEA). To quantify the number and location of preferred retinal loci (PRL), the kernel density estimator and expectation maximization for mixtures of gaussians were used.

Results. Patients have worse fixation stability than controls and large BCEAs resulted in more than one PRL. It was found that central field defects (10°) have negative correlation with the size of BCEA. In addition, the meridian of saccades during fixation was correlated with the meridian inter-PRL.

Conclusions. Patients with juvenile MDs have large BCEAs, frequently associated with two PRL. Similar results had been found for patients with age-related MDs. Also, the meridian of involuntary saccades during fixation was found to be correlated with the location of PRLs, suggesting a useful role of these movements in alternating between them. (Optom Vis Sci 2007;84:852-858)

Key Words: fixation stability, preferred retinal locus, eccentric fixation, eye movements

When macular vision is totally or partly lost because of macular disease (MD), such as age-related macular degeneration (AMD), Stargardt's disease, or cone degeneration, patients develop the ability to fixate with extra-foveal areas, which are also called preferred retinal loci (PRL).¹⁻³ Early research suggested the existence of a unique PRL,¹ possibly associated with a shift in the oculomotor center.⁴ However, there is now ample evidence for the use of multiple PRL (in this text defined as PRLs) even in simple visual tasks, e.g., fixating a cross.^{2,5-8}

It has been suggested that the location of the eccentric PRL or PRLs is idiosyncratic because the control of eye movements underlying fixation is capable of extensive plasticity, such that the number and location of eccentric loci used may change to optimize some aspect of the visual function, e.g., visual acuity or the size of the visual field.² For example, it was found that during Scanning Laser Ophthalmoscope (SLO) calibration, patients were able to maintain fixation with just one PRL but when they needed to decipher letters they used more than one.⁸ The number and

location of PRL used can be affected by a variety of other factors such as size, location, depth and sharpness of the border of the scotoma,^{9,10} and also by illumination¹¹ and complexity of the visual task.^{7,9}

Patients using eccentric PRL also have an increased number of saccades and consequently poor fixation stability.^{1,2,4,12} The role of these eye movements in the vision of patients with MD remains unclear.¹³ In a recent study patients were asked to decipher letters using eccentric retina while they voluntarily made saccades between two points of reference, and an enhancement of the letters was reported.¹⁰ Deruaz et al. suggested that saccades may be valuable in improving text perception in patients with central scotomas.¹⁰ In contrast, after improving the control of saccades, patients were able to read faster.^{5,14} This effect could be due to saccades suppression due effective use of a PRL, or a combination of factors.

Some researchers have studied eye movements in patients with MD^{15,16}; however, their relationship with PRL or PRLs was not examined.^{13,16}

TABLE 1.

Visual acuity, visual field defects (dB), and the mean value of BCEA obtained for each patient

	AM	AO	DN	JM	JF	JU	MO	PA	PG	SP
Visual acuity (log MAR)	0.9	0.9	0.8	1.0	0.8	0.7	0.7	1.0	0.8	0.9
CVFD (dB)	16.14	9.65	27.60	28.76	12.53	10.60	9.30	10.60	2.50	8.88
SCVFD (dB)	3.69	4.89	31.78	24.78	9.60	1.24	2.89	8.81	1.45	1.60
BCEA-10 s (arcmin ²)	2060	28995.7	23512.3	12137.6	5856.3	3806.2	37530.0	27785.2	48144.0	30516.0
BCEA-60 s (arcmin ²)	8698.2	30640.3	28826.7	16769.0	25932.3	5840.9	31713.0	43572.0	68294.3	44162.0

The values of the visual field defects are divided in two eccentricities: 0°–10° (CVFD) and 10°–30° (SCVFD). The last two rows are the averages of BCEA obtained for 10 s and 60 s for each patient.

In this work, eye movements during static fixation were recorded from a group of patients, with juvenile MD and from a group of controls. The purpose of this study was to characterize fixation and to define correlations between PRLs location and the meridia of eye movements. Results of this study may be of importance for a better understanding of eccentric fixation in patients with early macular lesions.

METHODS

Eye Movement Recordings

Eye movements were recorded with a modified infrared xy-gaze-tracking device (iView, SensoMotoric Instruments GmbH) at a sampling rate of 50 Hz and angular resolution of 0.2°. The fixation target was displayed on a 15-in CRT screen and consisted of a white cross of 2.5° with an open 1.25° center; the shape of the fixation target was similar to the diamond stimulus of fixation of the Octopus perimeter. Recordings were carried out in a dimly illuminated room. Observers were seated in a comfortable chair in front (50 cm away) of a computer monitor and rested their head on a chin rest. Their head movements were minimized by two additional restrains pressed against each side of the head. Recordings were made with the better eye while the opposite eye was occluded.

At the beginning of each trial the system was calibrated using a grid of 3 × 3 points (each point was a solid cross with 1.25°). Each point was presented in turn during a maximum of 6 s (this time was important to allow patients to localize the target). Patients were instructed to make a movement with the finger when they were fixating the calibration point. Simultaneously the experimenter accepted, manually, the point. Immediately after calibration of all points the eye-tracker software popped up a message informing if the eye-tracker had been successfully calibrated, if not, the calibration was repeated. After successful calibration the four extreme corners and the central point of the calibration grid were presented (in turn during 6 s) and eye positions were recorded for further visual inspection. After that the fixation target was presented. During fixation observers were instructed to keep their eyes as still as possible while fixating on the center of the target. Eye positions were recorded for 60 s. Data were validated postacquisition using the same procedure as in postcalibration. Each observer performed a total of 10 trials, with no more than three in each session. After offline visual inspection, a subset of three trials with the best calibration was selected and considered for further analysis. All the results presented in this article are based on these selected data.

Visual Fields

Monocular central and semicentral visual fields were assessed with an Octopus (Model 101) field analyser using the threshold routine Low Vision Program. Incremental target intensities were presented in a random order at 75 positions (10° ≡ 17 positions; 10° to 30° ≡ 58 positions) over a visual field of 30° around the macula. The test stimulus subtended 1.7° and was presented for 200 ms. The Octopus 101 is equipped with a camera, which allows fixation to be monitored during visual field examination. The relative visual field defect for each patient was computed by subtracting individual sensitivity from the average sensitivity from controls. Central visual field defects (CVFD) correspond to the average depth of field loss for the 17 positions tested within 10° and semicentral visual field defect correspond to the average depth of field loss for the 58 positions tested between 10° and 30°. These values are shown in Table 1.

Subjects

Ten patients with a diagnosis of juvenile MD, confirmed by at least two physicians, were selected. Nine were diagnosed with Stargardt's disease and one with cone dystrophy. They had a complete ophthalmologic examination with pupil dilation, fundus photography, and visual field exploration within the period of 1 year before this study. Immediately before the present study visual acuity was measured using a chart with a logMAR scale and HOTV optotypes (Precision Vision) and the values obtained were compared with values obtained during the previous year. Only patients with the same line of visual acuity in both assessments were selected. An equal number of controls with healthy eyes were selected. The mean age of the patients was 38.6 years (range 22 to 60, three women and seven men) and that of the controls was 32.7 years (range 22 to 54, three women and seven men). Best corrected visual acuity among patients was on average 0.85 log MAR (range 0.7 to 1.0) and 0.0 log MAR for controls. Informed consent was obtained from all participants and the research was conducted according to the guidelines promoted by the Declaration of Helsinki.

Eye Movement Analysis

Eye movements were divided in saccades and drifts. Velocity (*v*) and acceleration (*a*) were calculated using Eqs. 1 and 2, respectively.

$$v_i = \frac{\sqrt{(x_i - x_{i+1})^2 + (y_i - y_{i+1})^2}}{0.02},$$

for $i = 1, 2 \dots (n - 1)$ (1)

$$a_i = \frac{v_i - v_{i+1}}{0.02}, \text{ for } i = 1, 2 \dots (n - 2) \quad (2)$$

where n is the number of samples, x and y are the horizontal and vertical positions, respectively.

The onset of a saccade was determined when the acceleration reached $1000^\circ/\text{s}^2$ and the offset when the velocity reached $15^\circ/\text{s}$ ¹⁷; the amplitude of each saccade was defined by the distance between the onset and offset positions. Due to instrumental limitations small saccades were not detected.¹⁸ This limitation is referred every time it is considered important. Data 0.25 s before a blink and 0.5 s after, outliers, and saccades contaminated by blinks or by outliers (eye positions recorded outside the calibration area) were discarded. The remaining data were considered drifts. The dominant meridian for drifts and saccades and amplitude for saccades was also computed. The resultant meridian was determined using a slightly different version of the method described by Whittaker et al.² The meridia of movements were divided into six equally separated intervals between 0° and 180° . All movements with directions belonging to a certain 30° interval contributed equally for the resultant vector centered in the interval (from 15° to 165°) independently of their position in the interval. The resultant direction (for drift and saccades in each trial) was calculated adding tip-to-tail the vectors obtained after the previous division. Thus, the final meridian for each trial represents an average of the meridia. The magnitude of the resultant vector is inversely related to directional variability of the class of movement, in our study that magnitude was always different from zero.

Bivariate Contour Ellipse Area (BCEA)

Fixation stability was assessed using the concept of BCEA, which corresponds to the area expressed in arcminute² of the ellipse of isoprobability of fixation position.^{19–21} Let σ_H and σ_V be the standard deviation of gaze position in the horizontal and vertical directions, respectively, ρ the product-moment correlation of these two variables and k a parameter dependent on the probability area chosen. BCEA is defined as:

$$BCEA = 2\pi k \times \sigma_H \times \sigma_V \times \sqrt{1 - \rho^2} \quad (3)$$

The value of k was assumed to be 1.14, which corresponds to a BCEA where the fixation point would be found 68.3% of the time.²⁰

PRL Analysis

The number of PRLs was estimated using the concept of probability density estimation, which computes an estimate of the gaze distribution from the set of acquired data. Essentially the density estimator, in our case the function was kernel density estimator (KDE), is a function of known data that is used to estimate the unknown parameters of the distribution. The KDE corresponds to a sum of bumps placed at each observation; the shape of these bumps is determined by

the kernel function. The mathematical details were described elsewhere.^{6,22} In this work the KDE was used to estimate the parameters underlying a set of bivariate data. To maximize information (graphical visualization) about the distribution the smoothing parameters were set at the optimum level as recommended by similar analysis.^{6,22} The expectation maximization (EM) algorithm is a method of calculating maximum likelihood estimates. EM, also called the maximum likelihood method, is the procedure of finding the value of one or more parameters for a given statistics, which makes the known likelihood distribution a maximum. The EM iteratively estimates the locations and spreads of individual Gaussian models within a mixture. Its control function is the total likelihood and the mathematical details were explained elsewhere.⁶ In the present work EM was initialized with the number of models (PRLs) and the locations suggested by visual inspection of the graphical representation of the probability density estimation. The start parameters (start means) were approximated by the coordinates of the observed peaks, the spreads were common to all models, equal to standard deviation of x and y . Prior probabilities were uniformly distributed for all the models (e.g., 0.5 for two models or 0.33 for three models).

The algorithm ran a maximum of 200 iterations. The results obtained gave the locations and spread of each PRL and the correspondent probability. The distances between different PRLs and the connecting meridian were subsequently computed.

To define separated PRLs two criteria were used: one probabilistic and one spatial. The probabilistic criterion assumed that the probability associated to each PRL has to be equal or greater than 0.1.⁶ The spatial criterion assumed the minimum distance between PRLs is 1.86° . We assumed that the minimum distance between PRLs must be equal or greater than the median amplitude of saccades found among the patients. To test the coherence of the method the EM was applied to controls; nevertheless, considering similar criteria no PRLs were found. For the reasons referred in the end of section Eye Movements Analysis, this amplitude can be affected by a certain degree of imprecision, but considering the normal amplitude of microsaccades and drift,²³ this distance ensures that PRLs found are not a result of the normal variations of the eye position during fixation. Also, this criterion is justified by the underlying assumption that saccades have the function of change and/or recapturing the image to the PRL.^{1,10} When two distinct PRLs were found the possibility of a third PRL was tested.

Statistical Analysis

Nonparametric Spearman correlations were used to assess the correlation between variables within the group of patients or the control group. Nonparametric Mann-Whitney rank sum test was used to compare parameters between the two groups, where appropriate. Statistical tests were significant at the 0.05 level; in text p values are shown when $p \geq 0.05$ and the r or z values are shown when $p \leq 0.05$.

RESULTS

Fixation Stability

Fig. 1 represents the BCEA values for the first 10 s and for the complete trial (60 s) for patients and controls. The vertical bars indicate the maximum and the minimum values included in the

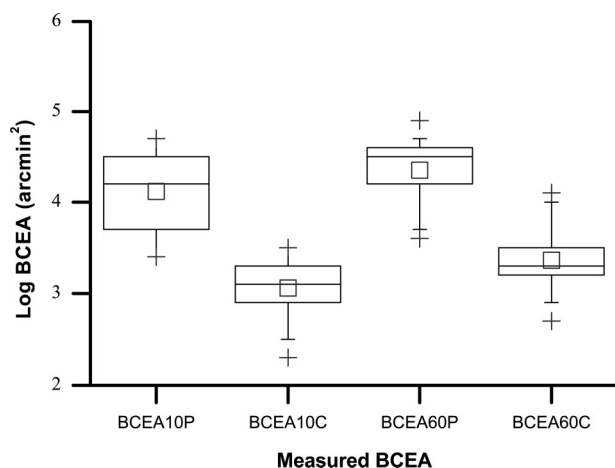


FIGURE 1.

The boxplot shows the values BCEA for the two groups of participants (logarithmic values). BCEA values were calculated for partial 10 s and total 60 s time of the trials. BCEA60P and BCEA10P are the values for patients for complete and partial trials, respectively. BCEA60C and BCEA10C are the values for controls for complete and partial trials, respectively. Outliers are signaled by crosses. The vertical bars indicate the maximum and the minimum values included in the calculation of median and mean. The median and mean values are signaled, respectively, by the horizontal line and the square symbol in the box. Inside the limits of the box are the 25 to 75 percentiles.

calculations of median (horizontal line) and mean (square symbol). The box defines the 25 to 75 percentiles. Crosses represent outliers. For the first 10 s of the trial the average BCEA was 19,614 arcminutes² (range 2652 to 53,183 arcminutes²) and 1418 arcminutes² (range 187 to 3518 arcminutes²) for patients and controls, respectively. For the complete trial (60 s) the average BCEA was 28,631 arcminutes² (range 3960 to 78,137 arcminutes²) and 3023 arcminutes² (range 495 to 13,289 arcminutes²) for patients and controls, respectively. The BCEA for controls was found to be significantly smaller than the BCEA for patients (Mann-Whitney test, $z = -6.29$ and $z = -6.44$ for 60 s and 10 s, respectively). These values of BCEA for patients were consistent with those obtained in other investigations.^{3,5,24,25} The values of BCEA for controls were larger, if compared with previous values obtained with normal sighted subjects.^{24,26} This is related to the extra-foveal characteristics of the target and not to its shape.^{24,26} The sampling rate of the instrument used to record the eye movements does not influence the values obtained for BCEA²⁰; however, saccades with amplitude below 0.4° not were detected because their amplitude was inferior to the minimum distance required by our criterion.

Fixation Stability and Field Defects

The correlation between CVFD and BCEA was analyzed and a significant negative correlation was found (10 s, $r_s = -0.75$; 60 s, $r_s = -0.69$). The correlation between semicentral visual field defect and BCEA was not significant. These results suggest that patients with more deep defects, in the central 10° of the visual field, have smaller values for BCEA. Previous studies did not report this

correlation, but different classifications of visual field defects were used.^{1,5}

PRL Computations

Fig. 2 shows two examples of the KDE results for a patient, PG. A multimodal (mostly bimodal) aspect, similar to those represented in the figure, was obtained for patients and for some controls. However, it was found that these local maxima are not always separable and only a single PRL was found. Two or more PRL were found for nine of the patients.

Table 2 summarizes the results concerning PRLs. Represented are the number of trials with PRLs and their characteristics (distance between mean values and meridian), the results for saccades (preferred meridian) and drifts (preferred meridian) obtained in trials with PRLs. Patient JU revealed fixation behavior similar to controls, despite having low vision. However, PG who has relatively good visual acuity exhibited the worst fixation behavior. In the case of PG extra factors observed during the trials, e.g., motivation/alertness, may have contributed to very pronounced fixation instability. Similar outliers were observed by other researchers.¹⁶

Fig. 3 gives examples of histograms representing the meridia of eye movements corresponding to three trials of 60 s fixation for one patient, AO. Fig. 3A shows the distribution of the drifts meridia and Fig. 3B represents the saccades meridia, each column covers a 30-degree angle. This example shows that drifts meridia do not have noticeable tendency, whereas the meridia of saccades have clear preferred orientations in two out of three trials. Significantly, the inter-PRLs meridian and the meridia of saccades had a significant positive correlation, $r_s = 0.56$. However, the inter-PRLs meridian and the meridia of drifts were not significantly correlated, ($p = 0.415$).

DISCUSSION

The present work investigated fixation in patients with visual field defects originating from juvenile MD and established correlations between visual fields and fixation stability. Also analyzed was the existence of PRLs and their correlations with eye movement meridia. The major findings were (i) a negative correlation between the central visual field defect and the stability of fixation, (ii) an enlargement of fixation areas for patients, (iii) the existence of two or more PRLs for most of the patients, and (iv) the existence of correlation between saccades meridia and PRLs locations.

Early investigations established that fixation instability increases for eccentric targets¹⁹; similarly, patients with eccentric PRL have enlarged fixational areas.^{1,2,5,27} The enlargement of fixation areas found in the present work for patients with juvenile MD is in agreement with those obtained for patients with other macular disorders, mainly AMD.^{3,6,24,28} Although correlations between visual field defects and fixation stability were not found in other studies,^{1,4,5} here a significant negative correlation between CVFD and fixation was found. An explanation for this correlation can be advanced; indeed, small areas inside the scotoma (one PRL) can be used to identify small targets and another PRL, eccentric to the scotoma, used to identify larger ones.⁸ This suggests that patients with more depressed visual fields can have a well-established PRL

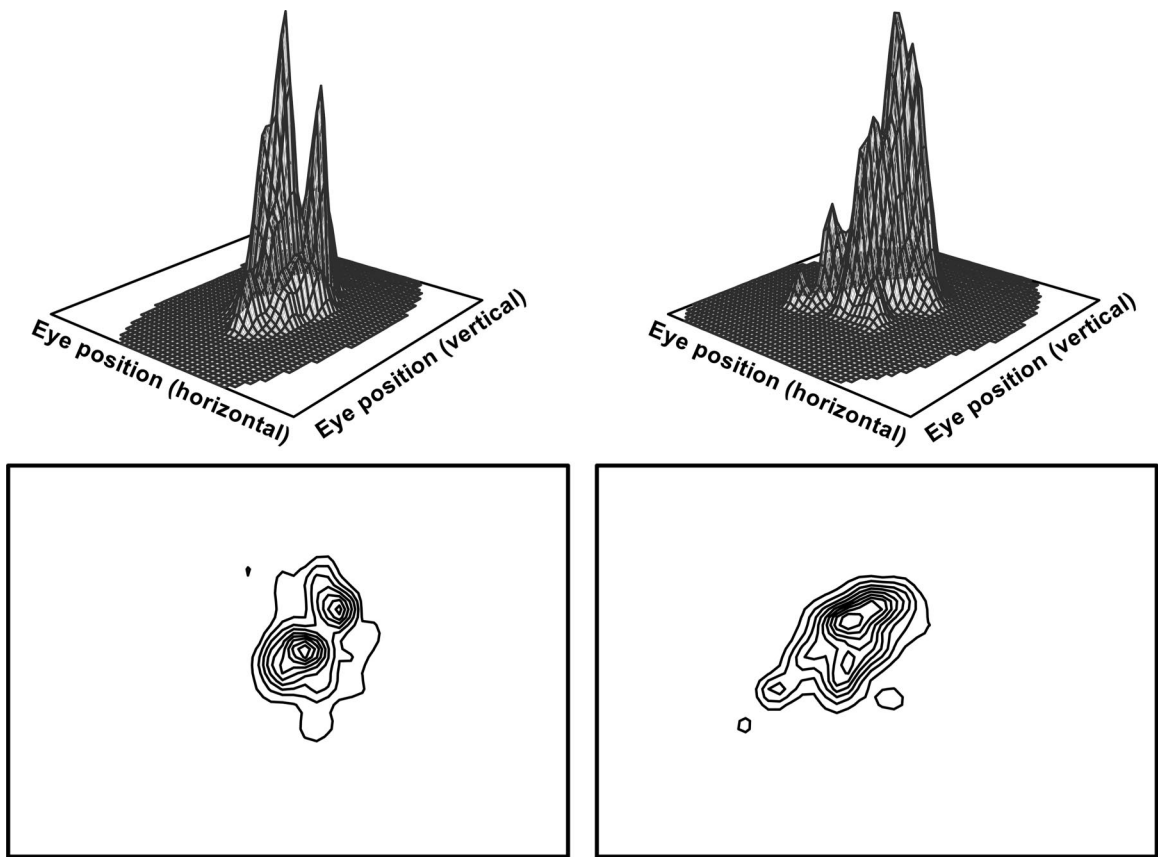


FIGURE 2. Two examples of KDE results for a patient in different trials. The graphic below and the immediately above represent the same values in different dimensions, 3D above and contour 2D below. The screen resolution, where the stimulus was presented (720 × 540), was divided in a 50 × 50 grid. The x axis corresponds to the horizontal axis of the monitor and the y axis to the vertical axis of the monitor. Inside each cell of the grid is the sum of KDE value associated with each pair of coordinates (x, y) belonging to that cell.

TABLE 2. The characteristics of the individual saccades and their relationship with PRLs in trials where different PRLs were found

Patient	No. trials with PRLs	Meridian of saccades (°)	Meridian of drifts (°)	2 distance (°)	PRLs meridian (°)	3 distance (°)	PRLs meridian (°)
AM	1	105.0	112.7	2.0	87.3	—	—
AO	1	52.0	76.8	2.5	30.6	—	—
DN	1	100.0	124.4	1.9	24.9	—	—
JM	1	134.8	123.4	3.8	156.4	—	—
JF	1	82.4	104.1	5.2	69.6	—	—
JU	None	—	—	—	—	—	—
MO	1	45.0	92.4	3.2	46.6	—	—
	2	72.3	100.0	2.6	55.8	—	—
	3	53.8	98.5	1.9	34.4	—	—
PA	1	111.2	93.2	2.6	49.2	—	—
PG	1	89.5	98.1	4.5	80.8	0.0–2.8–6.9 ^a	—
	—	—	—	—	—	2.8–0.0–4.7 ^b	—
	2	52.1	99.7	2.8	26.1	—	—
	3	85.6	109.0	3.5	59.7	0.0–2.5–3.5 ^a	—
	—	—	—	—	—	2.5–0.0–5.0 ^b	—
SP	1	89.1	98.1	1.9	86.9	—	—

^aThe values of the distance between the first PRL and the other two for two cases where three PRLs were found.

^bThe values of the distance between the second PRL and the other two, the first and the third.

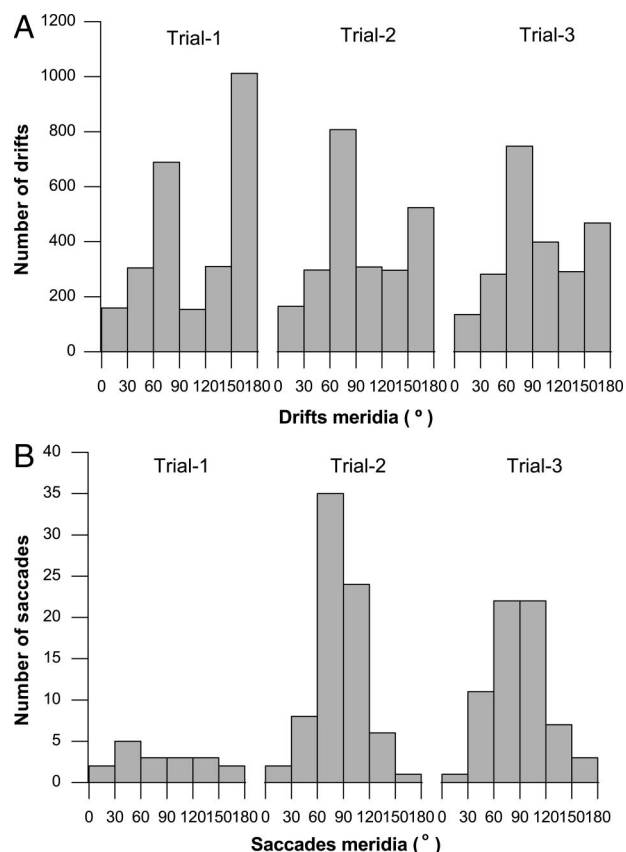


FIGURE 3.

Two histograms constructed for determining the dominant meridian for drifts (A) and saccades (B) in each of the three trials for a patient. Column heights represent the total number of movements whose meridia are inside the limits of each interval. For the determination of the dominant meridian the polar components of these vectors were calculated and added.

inside their lesion and use it all the time when fixating a static target. Consistent with this interpretation, two patients (AM and JF) in this study with the most depressed visual fields (Table 1) had a tendency to use just one PRL (Table 2). The existence of PRLs during static fixation has been frequently reported^{2,6}; nevertheless, the number of PRLs can be affected by some factors. Due to different experimental conditions and fixation analysis some studies found a single, enlarged, PRL.¹⁵ In our study nine out of 10 patients used more than one PRL. However, patients AM, JM, JU, and JF, whose BCEA values were below the median value for all patients, showed a tendency for a single PRL and only occasionally two (just in one of three trials). The target in this experiment was large, high contrast, and the task was simple. These are factors contributing to the relative low values of BCEA, and consequently single PRL, in some patients.⁸ For different subjects we found variability in behavior possibly related to factors not easily quantifiable, such as fatigue or alertness/motivation deficits. One piece of evidence for these factors are the higher values of BCEA obtained for 60 s when compared with the first 10 s of the trial, shown in Table 1. Other factors inducing variability in the number of PRLs found are the technique used to monitor fixation, instructions to patient, data analysis (PRL separation criterion), and task duration. In our experiment the learning effect cannot be evaluated because the data were recorded in different sessions with long

breaks (more than 2 weeks in many cases), also the best results obtained for different observers are distributed for all sessions. A large variability between trials was observed similarly to previous research.^{20,29}

Recent studies point to the usefulness of saccadic training in the improvement of reading speed,^{14,30} this study has established a concrete relation between meridia of saccades and PRLs. In conjunction these results suggest that during eccentric fixation a mixture of movements occurs, both effective and ineffective, that makes the peripheral retina usable; however, we acknowledge that others studies are necessary to confirm this finding.

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